A case report of Adult Onset Still's Disease and Kikuchi Fujimoto lymphadenitis-challenges and learning points

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ABSTRACT

Background: Adult Onset Stills Disease (AOSD) and Kikuchi Fujimoto Lymphadenitis (KFL) are both rare Rheumatological diseases. Co-occurrence is very rare.

Case Presentation: This is a case of AOSD and KFL co-occurrence presenting with polyarthritis, rash, and B Symptoms. Elevated serum lactate dehydrogenase and ferritin with anemia and lymphadenopathy raised suspicions of lymphoma. Histology confirmed KFL and clinical features, and raised ferritin confirmed AOSD.

After starting sulfasalazine, the patient was admitted to the hospital with 'Drug Reaction with Eosinophilia and Systemic Symptoms' (DRESS) Syndrome. Prior to sepsis exclusion, Gentamicin was given and subsequent hearing loss was noted.

Sustained remission was achieved with Tocilizumab and azathioprine. Tocilizumab was stopped during pregnancy.

Conclusion: The diagnostic challenges of two rare overlapping Rheumatological diseases are highlighted. An early distinction of disease flares or drug reactions from sepsis is difficult. Risk-benefit ratio consideration of continuing successful treatments in pregnancy is acknowledged.

Keywords: Case report, adult onset still disease, Kikuchi Fujimoto lymphadenitis, rare rheumatology diseases, DRESS syndrome, sulfasalazine, Disease Modifying Anti-Rheumatic Drugs, anti-tumour necrosis factor, interleukin (IL)-1 inhibition, IL-6 inhibition.

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Background

In this case, we present the rare co-occurrence of two systemic inflammatory disorders: Adult Onset Stills Disease (AOSD) and Kikuchi Fujimoto Lymphadenitis (KFL). We pay homage to the pitfalls in diagnosing each additionally complicated by their co-existence. We also discuss specific management strategies and their complications with consideration given to the added complexity of peripartum management where the risks and benefits are less certain.

AOSD is a systemic rheumatological disorder first described by Bywaters [1]. The cardinal features include periodic fevers, a characteristic salmon-colored cutaneous rash, and arthralgias. Diagnosis requires the satisfactory exclusion of both infection and malignancy. The Yamaguchi et al. [2] Criteria remain the most validated diagnostic criteria for AOSD, with 96% sensitivity and 92% specificity. Additionally, a markedly raised ferritin is useful [3]. Owing to the saturation of ferritin glycosylation in AOSD the percentage of glycosylated ferritin can also be a diagnostic aid. A glycosylated ferritin fraction of less than 20% is included in the Fautrel et al. [3] Criteria, with 80.6% sensitivity and 98.5% specificity. Treatment options include corticosteroids, Disease Modifying Anti-Rheumatic Drugs (DMARDs), and biological agents.

KFL, first described in 1972, is a benign self-limiting disease characterized by histological findings of histiocytic lymphadenitis [4]. KFL presents with fever, lymphadenopathy, and raised inflammatory markers [4]. Raised lactate dehydrogenase (LDH) can lead to confusion with lymphoma [5]. Where a classical, histological investigation is usually diagnostic and management is largely supportive. However, it is useful to monitor patients with KFL, as it is occasionally a harbinger of Systemic Lupus Erythematosus [6].

In the rare incidences where co-occurrence of AOSD and KFL have been reported ($n = 9$) [7], it has been postulated, based on responses to targeted biological therapies, that interleukins (ILs) 1 and 6 play an important role in the pathogenesis of both diseases [8].

Case Presentation

We present the case of a 27-year-old British born female, of Pakistani descent, with no preceding medical problems.

Her initial presentation was of a painful swollen right knee which was managed with rest and ice packs. She then presented with asymmetrical polyarthritis, drenching night sweats, and recurrent fevers.

A comprehensive infection screen was done including blood cultures, hepatitis (A, B, C), HIV, tuberculosis (QuantiFERON TB gold), Lyme disease, Ebstein Barr Virus, and Cytomegalovirus blood screens; all of which were negative. A transthoracic echocardiogram showed no signs of infective endocarditis nor had she clinical stigmata of this disease. Furthermore, she underwent a Positron Emission Tomography scan with no convincing pathology. An elevated serum LDH level, of 868 iu/l (NR 0-250iu/l) in combination with a high ferritin level of 5,784 ug/l (NR 30-400 ug/l) and microcytic anemia (MCV 73fl; Hb 103 g/l) raised a suspicion of lymphoma. CT imaging demonstrated small volume cervical and axillary lymphadenopathy which was further investigated with excisional lymph node and bone marrow biopsies. The lymph node biopsies were also culture negative for TB. Other investigations of note on initial hospital admission included: erythrocyte sedimentation rate 90 mm/hours, C-reactive protein (CRP) 224 mg/l, and negative rheumatoid factor, anti-citrullinated protein antibodies, and antinuclear antibodies.

The hematological investigations focused on the possibility of lymphoma.

Initial assessment of the axillary lymph node excision biopsy favoured early/proliferative phase KFL with a differential of T-cell lymphoma. The characteristic aneutrophilic necrosis with foamy histiocytes that is seen in established/late stage KFL was not present (Figures 1 and 2). Following further expert assessment and the finding of clonal T-cell receptor (TCR) gene rearrangement by polymerase chain reaction, a final diagnosis of Peripheral T-cell lymphoma unspecified was made. Bone marrow histology described as reactive, was non-contributory.

However, repeated clinical correlations concluded that this patient did not have lymphoma, and that the symptom chronology correlated with early phase KFL.

She was treated with low dose prednsiolone (5mg/D), which provided partial symptomatic relief of her fevers and joint pains. Four months after her initial symptoms, prominent cervical lymphadenopathy with tenderness and swelling of the hand, knee, and ankle joints were noted. An erythematous rash, not entirely typical of AOSD, was present over her posterior neck and sacral regions. Although AOSD was not diagnosed with certainty, as per the Yamaguchi Criteria, treatments for suspected AOSD and KFL were initiated. By this stage infection and malignancy were considered unlikely and 30 mg prednisolone/D and 200 mg hydroxychloroquine/D were given. After a further 4 months, she had ongoing active inflammatory arthritic symptoms with raised inflammatory markers and was reliant on prednisolone and non-steroidal anti-inflammatory drugs (NSAIDs). Over this period she had had two presentations to the Emergency Department and a limited response to intravenous steroids (I.V. methylprednisolone 500 mg/D for 3 days). Weekly methotrexate (10 mg/week) was introduced but discontinued after 2 months as it was implicated as a cause for recurrent urinary tract infections. Sulfasalazine was next initiated but within 2 weeks of starting it, our patient became severely unwell with a systemic upset in keeping with a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. Due to shared similarities (tachycardia, fever, and hypotension) with a presentation of sepsis, this diagnosis was established only after excluding infection. Recovery was seen after discontinuation of sulfasalazine. During her period of recovery, she reported dizziness and hearing impairment. Right-sided sensorineural hearing loss was confirmed. The hearing impairment was chronologically linked to aminoglycoside (gentamicin) antibiotic treatment given

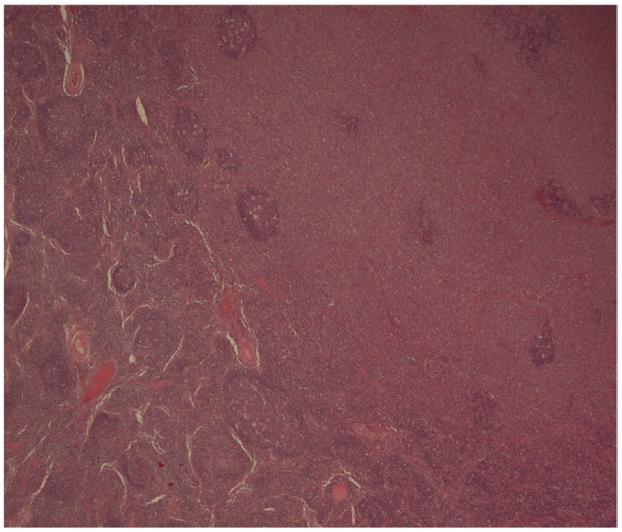

***Figure 1**. H&E × 2 Normal follicles on the left side, T-cell proliferation on right side.*

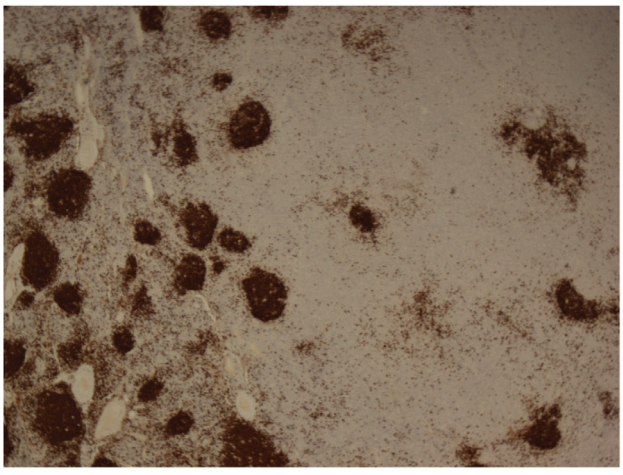

***Figure 2**. CD20 (× 2 objective) stains/highlights B lymphoid follicles with the expanded interfollicular T-cell zone being negative.*

Table 1. *Timeline.*

DATE	OCCURRENCE
Jun 2015	Presentation
Dec 2015	Started prednisolone and hydroxychloroquine.
Mar 2016	Methotrexate added.
April 2016	Methotrexate dose increased.
June 2016	Methotrexate replaced with sulfasalazine.
July 2016	DRESS secondary to sulfasalazine. Treated with gentamicin for presumed sepsis.
Dec 2016	Adalimumab added to prednisolone and hydroxychloroquine
Jan 2017	Hydroxychloroquine and adalimumab stopped. Azathioprine and tocilizumab commenced.
June 2017	Responding well to treatment
Feb 2018	Pregnant. Continued azathioprine, tocilizumab stopped.
Oct 2018	Uncomplicated delivery.
Jan 2019	Restarted tocilizumab and continues in remission.

during her hospitalisation before sepsis was excluded. Magnetic resonance imaging imaging of the inner ear did not highlight a structural pathology.

A difficult clinical course marked the ensuing 5 months and she had a severe relapse in her arthritis symptoms with an associated rise in her ESR to 58 mm/hour. Intra-articular steroid injections failed to provide adequate symptomatic relief. Azathioprine, 150 mg/D, and anti-tumour necrosis factor (TNF) therapy with Adalimumab, 40 mg subcutaneously/2 weeks were initiated, without clinical benefit after 3 months. Il-6 inhibition with Tocilizumab was then started and within 5 months she had achieved an excellent clinical response, with complete remission of her inflammatory arthritis and normalization of her ESR and ferritin. Eight months into her remission this patient became pregnant and despite the risk of her AOSD and inflammatory arthritis relapsing during pregnancy, we made the shared decision with our patient to discontinue Tocilizumab and to continue with azathioprine and prednisolone (5 mg/D). Tocilizumab was reserved for relapses. The treatment timeline is summarised in Table 1.

Discussion

This patient's clinical course illustrates the thorough investigations required in diagnosing AOSD complicated by the co-occurrence of KFL and the difficulty fulfilling the Yamaguchi criteria and excluding hematological malignancy and infection with certainty. This case highlights those challenges and problematic early consensus with histological interpretation. The initial assumption of lymphomatous disease was further confounded with a significantly raised ferritin, lymphadenopathy, and B symptoms (night sweats and fevers). Collaborative multi-professional assessments were required to discount malignancy and to confirm KFL.

Early exclusion of infection in such patients is crucial to avoid treatment delays. However, it is inevitable that in the early stages of presentation, patients with AOSD or DRESS will receive antibiotics until adequate investigations for sepsis have been undertaken to allow discrimination. In our case, we consider the administration of an aminoglycoside antibiotic for unproven sepsis to have resulted in this patient's sensorineural hearing loss.

The turbulent clinical course, we describe was characterized by an incomplete response to corticosteroid therapy and unsatisfactory responses to DMARDS.

Due to the low prevalence and heterogeneous nature of AOSD, with either systemic features of fevers, rash, and lymphadenopathy differing from a polyarthritis course, there are no randomised controlled trials on the treatment benefits or failures of DMARDs or biologic agents.

Our patient discontinued methotrexate due to recurrent urinary infections, however, methotrexate has been shown to control disease activity in NSAID naïve patients or those refractory to steroids and is the most prescribed DMARD in this context [10]. A small study (n = 13) demonstrated reduced or discontinued steroids in 60% who achieved remission, with regards to normalisation of CRP, ESR, WCC, and ferritin levels. Side effects of liver toxicity (15%) or acute interstitial pneumonitis (7%) were observed [9]. Fujii et al. [9] also noted that HLA–DR4 positivity confers a greater methotrexate response rate.

A 2014 review of steroid-refractory AOSD patients treated with methotrexate (n = 33) noted 33% developed side effects with deranged liver enzymes, cytopenias, or respiratory irritation or infections [10].

Frequent sulfasalazine side effects in treating AOSD, ranging from severe fulminant hepatitis, high fevers, hypotension, and myelosuppression to abdominal pain, vomiting, urticarial reashes, and facial flushing make this therapy less viable [11].Although hydroxychloroquine or azathioprine for AOSD is of unproven efficacy, the authors prescribed hydroxychloroquine as initial therapy for KFL as there are case reports suggestive of excellent responses [12]. Azathioprine was selected as a steroid-sparing agent due to its relative safety in pregnancy.

Consistent with our experience of AOSD refractory to adalimumab other reviews concluded that the total effect of anti-TNF (12.63%; infliximab: 6.8%, adalimumab: 1.4%, etanercept: 4.4%) was the lowest compared with other biologics (e.g., IL-1 antagonists, IL-6 inhibitors) [13].

As previously documented in patients with treatment-resistant AOSD who achieved a 76% remission rate with IL-6 inhibition [13], our case describes a very good clinical outcome with Tocilizumab.There is a paucity of controlled studies regarding tocilizumab safety in pregnancy, which raises anxiety with regards to continuation throughout pregnancy. The Roche Global safety database was analyzed for outcomes of tocilizumab given prior to or during pregnancy. Accepting the limitations of the review, including the concomitant use of methotrexate, it does not appear to increase the rate of malformations [14]. The authors recommend that the benefits of treating pregnant patients with this medication must be carefully weighed against any uncertain risks. IL-1 inhibition, in particular anakinra, but to lesser extents, canakinumab and rilonacept have also shown complete or partial remission in most AOSD refractory cases [15]. Although robust randomized controlled trials are awaited, a Delphi process undertaken to develop consensus recommendations on the use of these agents concluded very good efficacy [15].

Conclusion

This case stresses the challenges faced when two rare diseases coexist obscuring the diagnostic certainty of either. Aminoglycoside-induced sensorineural hearing loss, DRESS syndrome related to sulfasalazine in AOSD, and also the challenge of managing AOSD during pregnancy all require careful consideration. The observation that our patient's disease responded well to the IL-6 inhibitor Tocilizumab is in line with findings from previous case reports and highlights the importance of this cytokine in the pathogenesis of both AOSD and KFL, inspiring us to consider the value of further research.

What is new?

The treatment of Adult Onset Still Disease (AOSD) is still evolving and there is evidence that biological treatments, where necessary, are effective. The combination of Kikuchi-Fujimoto's disease and Adult onset Still's disease is very rare with very few case reports. The challenges of diagnosing and treating AOSD are often underrepresented in the literature.

List of Abbreviations

AOSD	adult onset Still's disease
CRP	C-reactive protein
DMARDs	disease modifying antirheumatic drugs
DRESS	drug eruption and systemic symptoms
ESR	Erythrocyte sedimentation rate
KFL	Kikuchi Fujimoto lymphadenitis
LDH	lactate dehydrogenase
TCR	T-cell receptor
TNF	Tumour necrosis factor
WCC	White cell count

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None.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this Case Report.

Consent for publication

Written informed consent was taken from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 27
2	**Final diagnosis**	Adult onset Still's disease and Kikuchi Fujimoto lymphadenitis.
3	**Symptoms**	Joint pain and swelling, fevers, night sweats, lymphadenopathy, erythematous rash.
4	**Medications**	Prednisolone, methylprednisolone, hydroxychloroquine, methotrexate, sulfasalazine, adalimumab, azathioprine, tocilizumab.
5	**Clinical procedure**	Lymph node biopsy, bone marrow biopsy.
6	**Specialty**	Rheumatology